2 8 SEP 2004

111

CLAIMS:

- 1. N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine (E1);N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine 10 (E2);N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E3);N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E4);15 N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E5); N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E6). N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] 20 glycine (E7). L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine (E10) D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine (E11) 25 L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine (E12) L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl]phenylglycine (E13) L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-30 phenylglycine (E14) N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E8). N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] 35 glycine (E9).
 - A compound according to claim 1 for use in medical therapy.

WO 2004/007430

5

35

- 3. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.
- A process for making a pharmaceutical composition comprising combining a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 5. A pharmaceutical composition comprising a compound according to

 claim 1 and at least one additional therapeutic agent selected from the group
 consisting of other compounds of formula I, anti-diabetic agents, antiosteoporosis agents, anti-obesity agents, growth promoting agents, antiinflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive
 agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants,
 bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents
 and retinoids.
- The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of a biguanide, a glucosidase inhibitor, a meglitinide, a sulfonylurea, a thiazolidinedione, a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR alpha/gamma dual agonist, an SGLT2 inhibitor, a glycogen phosphorylase inhibitor, an aP2 inhibitor, a glucagon-like peptide-1 (GLP-1), a dipeptidyl peptidase IV inhibitor and insulin.
- 7. The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone, englitazone, darglitazone, rosiglitazone and insulin.
 - 8. The pharmaceutical composition of claim5 wherein said additional therapeutic agent is an anti-obesity agent is selected from the group consisting of an aP2

WO 2004/007430



- inhibitor, a PPAR gamma antagonist, a PPAR delta agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor, a cannabinoid-I receptor antagonist and an anorectic agent.
- 9. The pharmaceutical composition of claim 5 wherein said additional therapeutic
 agent is a hypolipidemic agent selected from the group consisting of a
 thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG
 CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol
 absorption inhibitor, an ileal Na⁺/bile cotransporter inhibitor, a bile acid
 sequestrant and a nicotinic acid or a derivative thereof.
- 10. A method for preventing, inhibiting or treating a disease which is dependent on the expression of a T₃ regulated gene or associated with metabolic dysfunction, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.
- 11. A method for treating or delaying the progression or onset of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass, density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease, which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.
- The method as defined in claim 10 wherein the said disease is obesity,

 hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism,
 goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or
 skin disorders.
- The method according to claim 11 wherein the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis,





20

25

30

35

- Dernier's disease. eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
- 14. The method according to claim 10 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
 - 15. A method of treating or delaying the progression or onset of a skin disorder or disease which comprises administering to a mammalian patient a therapeutically effective amount of a compound as defined in claim 1 in combination with a retinoid or a vitamin D analog.
 - 16. A method for treating or delaying the progression or onset of obesity which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.
 - 17. A method according to claim 16 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.
 - 18. A method according to claim 17 wherein said anti-obesity agent is selected from the group consisting of aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor agents and anorectic agents.



- The use of a compound according to claim 1 in the preparation of a medicament to inhibit or treat a disease which is dependent on the expression of a T₃ regulated gene or associated with metabolic dysfunction.
- The use according to claim 19, wherein said disease is selected from obesity,
 hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism,
 subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass
 density or growth, eating disorders, reduced cognitive function, thyroid cancer,
 glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or
 disease.
- The use according to claim 20, wherein the skin disorder or disease is selected from dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
- Use according to claim 19 in combination with at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
- 30 23. Use according to claim 19 in combination with a retinoid or a vitamin D analog wherein said disease is a skin disorder or disease.
 - 24. Use according to claim 19 wherein said disease is obesity.
- Use according to claim ²⁴ in combination with at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.

5

26. Use according to claim 25 wherein said anti-obesity agent is selected from the group consisting of aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-I receptor antagonists, other thyroid receptor agents and anorectic agents.

10

30. A pharmaceutical composition which functions as a selective agonist of the thyroid hormone receptor comprising a compound as defined in claim 1.

15